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Direct Healthcare Professional Communication

Reminder of the Procoralan (ivabradine) conditions of use for the symptomatic treatment of chronic stable angina pectoris to avoid potentially dangerous bradycardia, while clinical trial findings are being evaluated

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA), Servier would like to inform you of an emerging safety issue for Procoralan (ivabradine). Preliminary results of the SIGNIFY study (**S**tudy assess**I**n**G** the morbidity-mortality be**N**efits of the $\mathbf{I_f}$ inhibitor ivabradine in patients with coronar**Y** artery disease) have shown a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo in a pre-specified subgroup of patients with symptomatic angina of CCS class II or more.
Initial data indicate that the adverse cardiovascular outcomes may be mostly associated with the target heart rate being below 60 bpm; however data from the SIGNIFY study are being further evaluated to fully understand its implications for the clinical use of ivabradine.

In the interim, to avoid potentially dangerous bradycardia, health care professionals are reminded of the following:

Summary:

- **Initial data indicate that the adverse cardiovascular outcomes observed in the SIGNIFY study may be mostly associated with a target heart rate below 60 bpm. Treatment must be discontinued if resting heart rate becomes too low or symptoms of bradycardia persist.**
- **The usual recommended starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.**
- **If resting heart rate decreases persistently during treatment or the patient experiences symptoms related to bradycardia, the dose must be down-titrated, including the possible dose of 2.5 mg twice daily.**
- **The dose should only be increased to 7.5 mg twice daily after three to four weeks of treatment if the therapeutic response with 5 mg twice daily is insufficient and if the 5 mg dose is well tolerated. The effect of a dose increase on the heart rate should be carefully monitored.**
- **Concomitant use of ivabradine with heart rate-reducing calcium channel blockers such as verapamil or diltiazem should be avoided.**
- **While on treatment with ivabradine patients should be carefully monitored for the occurrence of bradycardia or its symptoms (e.g. dizziness, fatigue or hypotension). Treatment of patients currently using ivabradine should be reviewed where appropriate.**

In addition, health care professionals are reminded of the following:

- **Ivabradine is authorised for the symptomatic treatment of chronic stable angina pectoris in adults with coronary artery disease and normal sinus rhythm.**
- **Ivabradine is not a first-line treatment, but is indicated:**
    - **in adults unable to tolerate or with a contra-indication to the use of beta-blockers**
    - **or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose resting heart rate is > 60 bpm.**

Further information on the preliminary findings from the SIGNIFY study:

The placebo-controlled SIGNIFY study was performed in patients with coronary artery disease without clinical heart failure. The ivabradine posology used was higher than the posology recommended in the ivabradine SmPC (starting dose of 7.5 mg twice daily (5 mg twice daily, if age > 75 years) and maintenance dose of up to 10 mg twice daily).

In the randomised set (n=19102), ivabradine did not significantly affect the primary composite endpoint (cardiovascular death or non-fatal myocardial infarction): hazard ratio 1.08, 95% CI [0.96–1.20], p=0.197 (annual incidences of 3.03% vs 2.82%). Similar results were observed for cardiovascular deaths (hazard ratio 1.10, 95% CI [0.94–1.28], p=0.249, annual incidences of 1.49% vs. 1.36%) and non-fatal MI (hazard ratio 1.04, 95% CI [0.90–1.21], p=0·602, annual incidences of 1.63% vs. 1.56%). No excess of sudden deaths was observed compared with placebo suggesting no ventricular proarrhythmic effect of ivabradine.

In the pre-specified subgroup of symptomatic angina patients (CCS Class II or more) (n=12049), a statistically significant increase in the primary composite endpoint was observed: hazard ratio 1.18, 95% CI [1.03–1.35], p=0.018 (annual incidences of 3.37 % vs 2.86 %). Similar trends were observed with the components of the primary composite endpoint, with a non-statistically significant difference between treatment groups in the risk of cardiovascular deaths (hazard ratio 1.16, 95% CI [0.97–1.40], p=0.105, annual incidences of 1.76% vs. 1.51%) and non-fatal myocardial infarction (hazard ratio 1.18, 95% CI [0.97–1.42], p=0.092, annual incidences of 1.72% vs. 1.47%).

In the safety set (n=19083), the incidence of bradycardia (symptomatic and asymptomatic) was high for ivabradine: 17.9 % vs. 2.1 % in the placebo group, with more than 30 % of the patients in the ivabradine group reaching a resting heart rate below 50 bpm at least once.
Initial analysis indicates that the adverse cardiovascular outcomes may be associated with the target heart rate being below 60 bpm; however study results are being further evaluated to fully understand the implications for the clinical use of ivabradine.

Ivabradine is also indicated in chronic heart failure NYHA class II to IV with systolic dysfunction, in patients in sinus rhythm and whose resting heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.
Healthcare professionals should take note of the relevant precautions in the product information for this indication, especially in relation to heart rate.

Call for reporting

Please report any suspected adverse reactions through the Yellow Card Scheme. The easiest way to report is online at www.mhra.gov.uk/yellowcard. Alternatively, complete a paper Yellow Card form which you can post to FREEPOST YELLOW CARD. Yellow Cards can be found in the BNF, MIMS or ordered by calling the Yellow Card Information Service Freephone on 0800 731 6789.
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Suspected adverse reactions can also be reported to SERVIER Laboratories Ltd
Email: pharmacovigilance@uk.netgrs.com Tel: 01753 666409

Company contact point
For further inquiries concerning this information, please contact the Medical Information Department of SERVIER in the UK
Tel: **01753 666409**

Email: **Medical.Information@uk.netgrs.com**

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Yours faithfully

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